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Case Report

Psychopharmacological Treatment of Prader-Willi Syndrome

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Abstract

Prader-Willi syndrome (PWS) is a genetic disorder caused by a mutation of chromosome 15, resulting in infantile hypotonia, obesity, short stature, mild-to-moderate mental retardation and neuroendocrinological abnormalities. A number of behavioral and psychiatric problems such as temper tantrums, self-injurious behavior, impulsiveness, lability of mood, attention deficit and hyperkinetic disorder symptoms, obsessive compulsive disorder and autistic spectrum disorder are associated with the syndrome. We report two adolescents with PWS who manifested psychiatric and behavioral problems and received psychopharmacological treatment. A 14-year-old boy had the uniparental disomy type of Prader-Willi syndrome and manifested attention deficit hyperactivity disorder symptoms, uncontrollable eating behavior and conduct disorder. A 15-year-old boy had the deletion type of PWS with attention deficit hyperactivity disorder symptoms and autistic spectrum symptoms. The two adolescents were both prescribed methylphenidate and sertraline hydrochloride. The present report shows the efficacy and side effects of psychotropic medications in Prader-Willi syndrome. (*Tzu Chi Med J* 2010;22(1):43–46)

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1. Introduction

Prader-Willi syndrome (PWS) is a rare genetically determined condition, which has an estimated prevalence of 1/10,000–1/15,000. The four genetic classes of PWS are: (1) maternal uniparental disomy (UPD) for chromosome 15; (2) 3–4 MB deletion of the paternally inherited 15q11-13 region; (3) paternally inherited balanced translocation involving this region; and (4) imprinting mutations or deletions of the PWS imprinting

center. Approximately 25–30% of patients with PWS present with UPD for maternal chromosome 15 and 60–70% of patients have deletion of 15q11-13 on the paternal chromosome [1–5].

PWS is now considered a multistage disorder characterized by three different phases [6]. The first phase, “the hypotonic phase”, is characterized by varying degrees of hypotonia during the neonatal and early infancy periods. The second phase, “the hyperphagic phase”, which usually starts between the age of 1 and

2 years, is characterized by a voracious appetite, hyperphagia, foraging for food, obesity, speech and articulation difficulties and cognitive dysfunction. In addition, individuals with PWS show significant maladaptive behavioral and emotional characteristics including temper tantrums, inappropriate social behaviors, skin picking, stubbornness, mood lability, impulsivity, depression, anxiety and obsessive-compulsive symptoms (7–10) and autistic spectrum disorder (11–13). Wigren and Hansen (2) reported that 22% of 58 individuals with PWS (aged 5–18 years) had significant problems with attention deficit, hyperactivity, impulsivity and some conduct problems. The third phase, “adolescence and adulthood”, is dominated by health problems secondary to obesity, including scoliosis, diabetes mellitus, and hypercholesterolemia (14). Approximately 10% of the adolescents and adults develop major psychiatric problems ranging from affective disorder to psychotic episodes (15–19).

Because of the numerous psychiatric illnesses in people with PWS, psychotropic medications such as antipsychotics, antidepressants and mood-stabilizing agents are often used (19). There are few reports (20,21) of methylphenidate use in PWS in patients with attention deficit hyperactivity disorder (ADHD) symptoms. We present two cases of adolescents given a combination of a psychostimulant (methylphenidate) and an antidepressant (sertraline hydrochloride).

2. Case reports

2.1. Case 1

Case 1 was a 14-year-old boy who was born after an uneventful pregnancy but was premature at 36 weeks of gestation and suffered from neonatal hypoxia. He walked at 2 years and 5 months, spoke his first word at age 3 years and spoke sentences at age 4 years. The results of chromosomal and molecular examination confirmed the diagnosis of PWS UPD. He also had diabetes mellitus controlled by metformin and glimepiride. His body weight was 54.2 kg and his body height was 155 cm. He was referred to the department of psychiatry because of conduct problems.

The patient had stolen bicycles, mobile phones and food even after being punished by his parents. He also told lies, denied every charge against him, and manifested repetitive speech, poor emotional control, temper tantrums and physical aggression toward his classmates. He showed poor attention and concentration, was easily distracted, had been very hyperactive for years and had become oppositional in the previous year. The Chinese version of the Swanson, Nolan and Pelham, Version IV scale for ADHD-parents (SNAP IV) was administered and he obtained a score of 17 in the inattention subscale (90–95th percentile), 10 in the

hyperactivity-impulsivity subscale (85–90th percentile) and 24 in the oppositional subscale (99th percentile) (22). In the Chinese version of the Wechsler Intelligence Scale for Children-III he had a full-scale IQ of 53, verbal IQ of 66 and performance IQ of 47.

The patient was diagnosed with ADHD, conduct disorder and mild mental retardation. Methylphenidate 18 mg one tablet per day (Concerta; Alza Pharmaceuticals, Mountain View, CA, USA) was initially prescribed and behavior modification using token economy was implemented to eliminate his conduct problems. Three months later, he had no more conduct problems. The Chinese version of the SNAP IV was administered again and he obtained a score of 5 in the inattention subscale (30th percentile), 5 in the hyperactivity-impulsivity subscale (65th percentile) and 8 in the oppositional subscale (80th percentile). However, owing to his skin-picking, temper tantrums and uncontrollable eating behavior, sertraline hydrochloride (Zoloft; Pfizer U.S. Pharmaceuticals Group, New York, NY, USA) was prescribed and his mother reported that he began to show better emotional control, and had less skin-picking behavior, but still ate too much.

One year later, he started to show self-talking and the severity of skin-picking increased. The symptoms subsided after discontinuation of methylphenidate. He remained on sertraline hydrochloride 50 mg 2 tablets per day for 6 months. He then began to have reference delusions in which some classmates insulted him and he manifested physical aggression toward his mother and classmates. Risperidone 0.5 mg was prescribed and his psychotic symptoms showed great improvement.

2.2. Case 2

Case 2 was a 15-year-old boy who was born via cesarean section after an uneventful pregnancy, but he had neonatal hypoxia. He spoke his first word at age 3 years and walked at age 4 years. Chromosomal and molecular examination established the diagnosis of PWS, deletion type. He received growth hormone therapy for half a year but treatment was discontinued because of hip complications. His body weight was 54.2 kg and his body height was 143.5 cm. He was referred to the department of psychiatry because of temper tantrums. A family history revealed that his father had bipolar illness.

The patient showed some autistic spectrum symptoms, such as poor social skills, lack of empathy, and repetition of behaviors and questions, and he repeatedly rearranged objects on his desk and changed clothes until he felt “just right”. He had temper tantrums if there were any changes in his daily routine. He also had stereotyped thinking, and excellent recall of telephone numbers and names. He showed poor

attention and concentration, was easily distracted, and had been very hyperactive and oppositional for years. The Chinese version of the SNAP IV was administered and he obtained scores of 19 in the inattention subscale (95–99th percentile), 23 in the hyperactivity–impulsivity subscale (over 99th percentile) and 24 in the oppositional subscale (over 99th percentile) (22). The Chinese version of the Wechsler Intelligence Scale for Children-III yielded a full-scale IQ of 55, verbal IQ of 69 and performance IQ of 48.

The patient was diagnosed with ADHD and mild mental retardation, and methylphenidate 18 mg one tablet per day (Concerta; Alza Pharmaceuticals) was prescribed. A follow-up administration of the Chinese version of the SNAP IV yielded scores of 16 in the inattention subscale (90–95th percentile), 19 in the hyperactivity–impulsivity subscale (95–99th percentile) and 14 in the oppositional subscale (95th percentile). His mother felt that his inattention and hyperactive symptoms had moderately improved. Five weeks later, because of temper tantrums and compulsive repetitive speech that disrupted his interpersonal relationships, sertraline hydrochloride 50 mg per day was prescribed. One month after administration of antidepressant medication, he began to have a decreased need for sleep, became hypertalkative, manifested an irritable mood and threatened his family with a knife. Medication-induced mood disorder (manic episode) was suspected and he was admitted to an acute psychiatric ward where carbamazepine 200 mg one tablet three times per day (Tegretol; Novartis Pharmaceuticals Corp., East Hanover, NJ, USA) was prescribed. After discharge, the patient remained on carbamazepine and methylphenidate for irritable mood and ADHD symptoms.

3. Discussion

Wigren et al (2) found that one fourth of patients with PWS show clinical indices of ADHD, which are highly associated with maladaptive conduct problems. Jerome (20) reported a case of PWS with marked features of attention deficit disorder, which was treated with methylphenidate 60 mg a day in divided doses. Methylphenidate has been widely studied among mentally retarded children with ADHD and in children with Fragile X syndrome (23).

Our patients with different types of PWS both showed ADHD symptoms diagnosed with the Chinese version of the SNAP IV. They were both treated with low dose methylphenidate (0.33 mg/kg of body weight) and both showed good responses in each of the three domains assessed by the SNAP IV scales, i.e. inattention, hyperactivity–impulsivity and oppositional domains. However, Case 1, who had the UPD type of PWS, later developed self-talking and increased severity of skin-picking and the symptoms subsided

after discontinuation of methylphenidate. Case 2, who had the deletion type of PWS, has remained on methylphenidate for inattention and impulsivity. Selective serotonin reuptake inhibitors are frequently used in PWS for several different psychopathologies, including skin-picking, food intake-related behaviors, depressive disorder and obsessive-compulsive symptoms (19).

The symptoms of poor emotional control and skin-picking in Case 1 were well-controlled by sertraline for more than 1 year, but he developed psychotic symptoms later. Studies by Boer et al (24) and Vogels et al (25) demonstrated a relatively high rate of affective psychosis in adolescents with PWS, especially in subjects with UPD.

After taking sertraline for temper tantrums for 1 month, Case 2 manifested an episode of suspected drug-induced mania, and carbamazepine was used to control his emotional dysregulation. Hergüner and Mukaddes (26) reported a case of fluoxetine-induced psychosis in a patient with PWS. After discontinuation of sertraline use, Case 2 did not show any episodes of mania and he has been able to attend a vocational high school. In a larger study of PWS in the United Kingdom (19), 24/85 (28.2%) individuals with the deletion type of PWS had a history of psychopathologies including non-psychotic depressive illness, depressive psychosis and psychotic illness. No one with the deletion type of PWS had bipolar illness. Thus, we suspect that Case 2 in our study might have had selective serotonin reuptake inhibitor-induced mania, probably associated with his family history of bipolar disorder.

In conclusion, PWS usually manifests numerous phenotypes, such as psychiatric symptoms ranging from autistic spectrum disorder to attention deficit hyperkinetic disorder, and from obsessive-compulsive, affective disorder to psychosis. Therefore, psychopharmacological treatment is important, but the side effects of medications must be carefully monitored because different psychopathologies might manifest themselves in the course of the illness.

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